PB80-216849

Diallate
Position Document 2/3

(U.S.) Environmental Protection Agency
Arlington, VA

Apr 80

U.S. Department of Commerce
National Technical Information Service
NTIS.

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO. EPA/SPRD-80/27	2.	3. Recipient's Accession No. PB 80 216849

4. Title and Subtitle
Diallate: Position Document 2/3

5. Report Date
4/80

6.

7. Author(s)

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
Special Pesticide Review Division
Environmental Protection Agency
Crystal Mall #2
Arlington, VA

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address
Environmental Protection Agency
401 M St. SW
Washington, DC 20460

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Risk/benefit analysis: qualitative & quantitative risks of a pesticide, value of crop uses, availability of alternative pesticides, exposure to man and environment. Identification of risk reducing regulatory options and proposed Agency action.

17. Document Analysis a. Descriptors

0504,0606,0703

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement: Unlimited	19. Security Class (This Report) Unclassified	21. No. of Pages
	20. Security Class (This Page) Unclassified	22. Price

(See ANSI-Z39.18)

See Instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

PB80-216849

DIALLATE
Position Document 2/3

April, 1980

Office of Pesticides and Toxic Substances

EPA/SARD - 80/27

Environmental Protection Agency
401 'M' Street, S.W.
Washington, D.C. 20460

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

ACKNOWLEDGEMENTS

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I. Background

A. Introduction

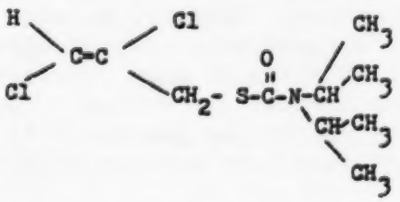
1. Organization of Position Document

This Position Document contains five parts. Part I is the introductory section. Part II is an evaluation of the risk of diallate. It includes descriptions of the relevant data on toxicity, exposure, and the Agency's present risk assessment. Part III is a summary of the economic benefits of diallate. Part IV describes the range of the regulatory options considered by the Agency. Part V puts forward the Agency's recommended option.

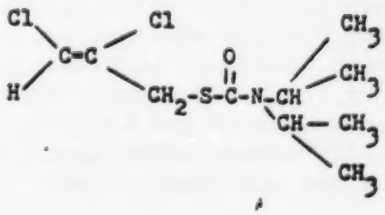
2. Chemical and Physical Characteristics

Diallate (S-(2,3-Dichloroallyl)diisopropylthiocarbamate) is a thiocarbamate which is also known by the trade name AVADEX®. Diallate acts as a pre-emergence selective herbicide. It is an amber-colored liquid which is formulated as an emulsifiable concentrate (4 pounds/gallon) and as a granular (10%).[1/] Its molecular weight is 270.2. Its structural formula is as follows:

Diallate trans isomer



cis isomer



Formula

$C_{10}H_{17}Cl_2NOS$

Formula Weight

304.7

3. Registered Uses

Monsanto Agricultural Products Company is the sole producer of technical-grade diallate. As a registered pesticide, diallate is currently used to control wild oats in sugar beets, flax, barley, corn (grain and silage), forage legumes (alfalfa, sweet, red and alsike clover),

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1/ As a granular, diallate is registered for use on sugar beets only.

lentils, peas, potatoes, safflower, and soybeans. In combination with pebulate or cycloate, it is used also to control other grasses and broad-leaf weeds in sugar beets. Diallate is incorporated into the soil in the fall before the freeze or in the spring, either before or after seeding, but before emergence. Usually only one application is made by the user per season.

Eight federal registrations of products containing diallate are held by three registrants.

4. Tolerances

Tolerances for diallate in or on raw agricultural commodities are listed in 40 CFR 180.277 as follows: negligible residues on alfalfa (fresh and hay), barley (grain, forage, and straw), clover (fresh and hay), field corn grain, fodder and forage, flaxseed, lentils, peas, pea forage and hay, potatoes, safflower seed, soybeans, soybean forage and hay, and sugar beet roots and tops at 0.05 part per million.

B. Applicable Sections of FIFRA

The Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. 136 et seq.), as amended, confers authority on EPA to regulate pesticide products. Section 3(a) of the Act requires all pesticide products to be registered by the Administrator before they may be sold or distributed. Before the Administrator may register a pesticide, however, he must determine that its use will not result in "unreasonable adverse effects on the environment," defined in Section 2(bb) of FIFRA to mean "unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." In other words, any registration decision must take into account both risk and benefits from the pesticide's uses.

Section 6(b) of FIFRA authorizes the Administrator to issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears to him that the pesticide or its labeling "does not comply with the provisions of [FIFRA] or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus, the Administrator may cancel the registration of a pesticide whenever he determines that it no longer satisfies the statutory standard for registration; this standard requires, among other things, that the pesticide "perform its intended function without unreasonable adverse effects on the environment" [FIFRA 3(c)(5)(C)]. He may also cancel the registration of a pesticide if its labeling does not comply with the misbranding provision of FIFRA, which requires the labeling to contain certain language "adequate to protect health and the environment" (FIFRA 2(q)).

C. The "RPAR" Process

To implement its authorized functions, the Agency has designed the Rebuttable Presumption Against Registration (RPAR) process, which involves gathering data on the risks and benefits associated with the uses of suspect pesticides. By allowing all interested parties to participate by submitting information, the process enables EPA to make balanced decisions concerning problem pesticides.

If the presumptions of risk are not rebutted, the evidence pertaining to benefits must be evaluated and considered together with the evidence pertaining to risk. Various risk reduction methods and their costs are analyzed. The Agency then determines whether the pesticide may be regulated so that a balance is achieved between risks and benefits. If the statutory balance cannot be reached for a use, the registrations for that use must be cancelled.

D. Regulatory History

The first registration for a product containing diallate was granted to Monsanto on December 9, 1960 (EPA Registration Number 424-119). Use of diallate on corn, forage legumes, lentils, peas, potatoes, safflower, and sugar beets was approved. Because no residues were detected in or on these raw agricultural commodities the use of diallate was accepted under the "no residue-zero tolerance" concept.

In 1954, the Food, Drug, and Cosmetic Act was amended to provide for the establishment of tolerances or exemptions from tolerances for pesticide chemicals in or on food crops. The amendments also provided for the establishment of a tolerance "at zero level" if data showed that no detectable residues were present in the treated crop at the time of harvest. In 1965 the National Research Council of the National Academy of Sciences recommended that the "no residue-zero tolerance" concept be abandoned. This recommendation was based on the fact that this concept, as applied in the registration and regulation of pesticides, had become scientifically and administratively untenable. Among the reasons given by the council were that analytical methodology had improved, and that small levels of pesticide residues had become detectable (Pesticide Residues Committee Report on "No Residue" and "Zero Tolerance", NAS-NRC, June 1965).

In 1966 the USDA began to phase-out this concept (FR April 13, 1966). Registrants of products under this concept were given (through a series of 1 year extensions) until 1971 to convert the "no residue" tolerances to finite tolerances.

The Council also recommended that pesticides previously regulated under the "no residue" concept be regulated on the basis of "negligible residue" tolerances. These tolerances could be established by supplying a limited amount of data. It was concluded that a negligible residue is the amount which will produce no effects in test animals, which (effects) are

indistinguishable from control animals. The tolerance, in many cases, may reflect the sensitivity of the method and require only two 90-day (subacute) animal studies. Such was the case when the tolerance for negligible residues was established for diallate.

During the phase-out period, Monsanto filed a petition (PP 7F0607) requesting a tolerance of 0.3 ppm on corn, forage legumes, lentils, peas, potatoes, safflower, and sugar beets. That petition was subsequently withdrawn and a second petition was filed (PP 9F832) requesting a tolerance for negligible residues of 0.05 ppm on the above crops. Tolerances for negligible residues of diallate were established in or on the above raw agricultural commodities on July 28, 1971 (40 CFR 180.277).

On May 31, 1977, the Agency issued in the Federal Register (42 FR 27669) a notice of rebuttable presumption against registration and continued registration of pesticide products containing diallate. Diallate: Position Document 1, published together with the RPAR notice, explained the background and supporting data for the presumption of risk cited in the RPAR notice.

Following the publication of the RPAR notice, Monsanto Company requested and was given a 60-day extension of the rebuttal period. The extension was granted to all registrants and interested parties.

E. Basis for the Rebuttable Presumption

The rebuttable presumption against registration and continued registration of pesticide products containing diallate was issued on the basis of oncogenic effects in test animals as a risk criterion [40 CFR 162.11 (a)(3)]. Specifically, the presumption was based on the following three long-term feeding studies which indicated that diallate is potentially oncogenic: 1) a National Cancer Institute (NCI) Ulland et al., 1973) rat study (Litton Bionetics), 2) an Industrial Bio-Test (IBT) (Keplinger. 1976a) rat study (sponsored by Monsanto Company), and 3) an NCI mouse study (Innes et al., 1969).

Data from the rat study conducted by Ulland and coworkers at Litton Bionetics were verified by the NCI and reviewed by the EPA Carcinogen Assessment Group (CAG). The CAG concluded that the Litton Bionetics study showed a statistically significant increase in malignant tumors at the highest dose in male rats and in carcinomas at the higher dose in female rats.

Industrial Bio-Test concluded from its rat study "that the neoplastic lesions noted in the test and controls were considered normal for rats of this age and strain." In its evaluation, the CAG concluded that "the Industrial Bio-Test study in rats showed a statistically significant excess of mammary carcinomas in females."

The CAG also concluded that the mouse study conducted by Innes and coworkers showed an increased incidence of liver-cell and pulmonary tumors. This study was the basis for the Mrak Commission Report recommendation that human exposure to diallate be minimized because there was evidence of tumor induction in mice.

Respondents were given an opportunity to rebut the presumption against diallate by showing (1) that the Agency's initial determination of risk was in error, or (2) that given current use patterns, exposure to diallate is not likely to result in any significant chronic adverse effects [40 CFR 162.11(a)(4)]. Respondents were also invited to submit evidence on behalf of the social, economic, and environmental benefits of the use of the pesticide [40 CFR 162.11(a)(5)(iii)].

II. Analysis and Assessment of Risk

A. Analysis of Rebuttal Arguments - for Oncogenicity

The Agency has analyzed the rebuttal comments submitted to it in response to to the presumption of oncogenicity[2/] and responded to these comments in this section. From the analysis of rebuttal comments, the Agency has concluded that the oncogenic presumption against diallate has not been rebutted and that humans are subject to the risk of developing cancer from the use of diallate.

1. Rebuttal Pertaining to National Cancer Institute (NCI) Rat Study (Litton Bionetics)

a. Errors in Tabulated Data

Monsanto Company noted errors in the data cited in the EPA's Carcinogen Assessment Group (CAG) (Albert, 1979) report and in rebuttal presented a retabulation of the raw data (Monsanto Co., #1A[30000/15]).

The Agency acknowledges Monsanto's rebuttal on this point. The CAG has re-evaluated the raw data and has corrected its report accordingly. However, these corrections do not change the Agency's interpretations of the study.

The CAG's revised tabulation of the data (shown in Tables II-1 and II-2) differs somewhat from the data presented by Monsanto. Most of these differences are due to the classification of gliomas and leukemias as sarcomas by the CAG and as carcinomas by Monsanto. These differences in classification are unimportant since the Agency bases its regulatory decisions on oncogenic risks which include all tumors (Albert, 1979a).

b. Statistical Difference in the Malignant Tumors in Males

Monsanto Company contended that according to their analysis of the data, there is no statistical difference in the number of malignant tumors in the diallate-treated male rats (both dose groups combined) compared to pooled controls (13/52 treated vs. 11/64 controls, $p = .21$). Monsanto asserted further that there is no statistical difference in the number of malignant tumors or of sarcomas in either treated group of male rats (high or low dose) as compared to control groups (Monsanto Co., #1A[30000/15]).

The respondent acknowledged an increased incidence of carcinomas in the high-dose male group as compared to the controls, but submitted that the incidence in the low-dose male group was not different from either control group (Monsanto Co., #1A[330000/15]).

2/ In addition to the above-mentioned rebuttals, the Agency received 16 responses pertaining to the benefits of diallate. Comments submitted on benefits are addressed in Section III, "Benefit Analysis."

Table II-1. NCI Rat Study, Incidence of Malignant Tumors in Male Rats Ingesting Avadex (Diallate)[a/]

Comparison of Low- and High-Dose Groups to Pooled Controls			
Dose Group	No. of Rats with Carcinomas	No. of Rats with Sarcomas[b/]	Total No. of Rats with Malignant Tumors[c/d/]
Pooled Control	4/64 (6%)	7/64 (11%)	11/64 (17%)
Low Dose	3/26 (12%)[e/]	1/26 (4%)	4/26 (15%)
High Dose	4/26 (15%)	4/26 (15%)	10/26 (38%)[f/g/]

a/ Revised CAG tabulation. (Albert, 1979a)

b/ Gliomas and leukemias were counted as sarcomas.

c/ Rats with carcinomas did not have sarcomas.

d/ Corrected for survival.

e/ Two of these rats with carcinomas had metastases (carcinomas of the prostate metastatic to lung and lymph nodes; islet cell carcinomas of the pancreas with metastases to the heart).

f/ The tumor incidence in the high dose group compared to the pooled control group is statistically significant ($p = .032$) (Fisher Exact Test).

g/ The total incidence of 10/26 includes 2 unclassified malignant tumors in the subcutaneous tissue.

Table II-2. NCI Rat Study, Incidence of Malignant Tumors in Female Rats Ingesting Avadex (Diallate)[a/]

Comparison of Low- and High-Dose Groups to Pooled Controls			
Dose Group	No. of Rats with Carcinomas	No. of Rats with Sarcomas[b/]	Total No. of Rats with Malignant Tumors[c/]
Pooled Control	3/64 (5%)	4/64 (6%)	7/64 (11%)
Low Dose	2/26 (8%)[d/]	2/26 (8%)	4/26 (15%)
High Dose	5/26 (19%)[e/]	0/26 (0%)	5/26 (19%)

a/ Revised CAG tabulation. (Albert, 1979a).

b/ Gliomas and leukemias were counted as sarcomas.

c/ Rats with carcinomas did not have sarcomas.

d/ The two rats with carcinomas of the mammary gland had metastases to the lungs.

e/ The tumor incidence in the high dose group compared to the pooled control group is statistically significant (p = .042) (Fisher Exact Test)

The Agency rejects Monsanto's rebuttal on this point. The CAG analyzed tumor incidence from each treatment group individually, whereas Monsanto Company combined the data from the high- and low-dose groups and in combining the data the significance found in the high dose group was masked. The CAG re-evaluation of the data demonstrated a statistically significant increase in total malignant tumors in male rats of the high-dose group as compared to pooled controls (10/26 treated vs.11/64 controls; p = .032) (Refer to Table II-1) (Albert, 1979a).

c. Statistical Significance of Carcinomas, Sarcomas, and Total Malignant Tumors in Females

From their analysis of the data on female rats, Monsanto Company concluded that there is no statistically significant increase in carcinomas, sarcomas, or total malignant tumors in either treated group (Monsanto Co., #1A[30000/15]).

The Agency rejects this rebuttal attempt. From the CAG's revised tabulation of the data, it is apparent that there is a statistically significant increase of carcinomas in the female rats of the high-dose group as compared to pooled controls (5/26 treated vs. 3/64 controls; p = .042). (Albert, 1979a.) (Refer to Table II-2.)

d. Low Number of Tumors in High-Dose Male Rats

Monsanto Company asserted that the number of tumor-bearing rats in each diallate-treated group is lower than in either control group, and emphasized that the high-dose group has the lowest number of animals with tumors (Monsanto Co., #1A[30000/15]).

The Agency rejects this point of rebuttal. The number tabulated by the CAG for the controls was 11/64 (17%) as compared with 10/26 (38%) and 4/26 (15%) in the high-and low-dose male groups, respectively. The individual numbers of animals possessing tumors is not relevant. The appropriate comparison is the percentage of animals which have tumors. The percentage of animals with tumors in the high-dose group is statistically greater than the percentage of animals with tumors in the control group. (Albert, 1979a.)

e. No Apparent Effect of Diallate on the Formation of Individual Tumor Types

Monsanto contended that an evaluation of individual tumor types/sites is necessary to conclude that a compound is carcinogenic, and that there was no apparent effect of diallate on the formation of individual tumor types (Monsanto Co., #1A[30000/15]).

The Agency rejects this rebuttal attempt. Although there was no statistically significant incidence of individual tumor types, there was a statistically significant increase of total malignant tumors in

male rats of the high-dose group relative to pooled controls. Moreover, there was a statistically significant increase of carcinomas in female rats of the high-dose group compared to pooled controls. The use of total tumor data in evaluating carcinogenicity is discussed in a recent Interagency Regulatory Liaison Group (IRLG) document as follows:

> "At the present time there is considerable uncertainty about the interpretation of carcinogenic responses in terms of the total tumor yield in contrast to the response in terms of a statistically significant increase of tumors in specific target organs or tissues. Traditionally, carcinogens have been recognized in human and animal studies by a decisive increase in tumors of target organs. However, it is conceivable that a generalized increase in total tumor yield, in the absence of an excess incidence in one or more target tissues, could occur, for example by a promoting effect that generally increases the spontaneous incidence of tumors in test animals or by the action of a multipotent carcinogen whose response did not reach statistical significance in any one organ even at the maximum tolerated dose.[3/]"

2. Rebuttal Pertaining to Industrial Bio-Test (IBT) Rat Study (Sponsored by Monsanto Co.)

The existing registrations and tolerances for diallate were established and supported by data contained in studies conducted by Industrial Bio-Test Laboratories (IBT) for Monsanto.

In 1977, subsequent to the publication of Position Document 1, the Agency, in the Office of Pesticide Programs, established a Toxicology Data Audit Program (TDAP) to assure the reliability and integrity of data supplied to the Agency by pesticide manufacturers. These data are the integral component of the information upon which pesticides are registered and tolerances are established in the United States.

Industrial Bio-Test Laboratories (IBT) was one of the initial laboratories audited jointly with the Food and Drug Administration. The IBT laboratory performed a large volume of testing utilized by the Agency in its regulatory decision-making. During an audit at the facility, numerous significant departures from acceptable laboratory practice were noted. As a result, the Agency decided to reevaluate all pivotal IBT studies used in support of tolerances. The workload of this evaluation program was shared with the Canadian Government in cases where chemicals were registered on identical data bases. The IBT studies for diallate were evaluated by Canada and the results are shown in Table II-2a.

3/ IRLG (February 6, 1979), Scientific Bases for Identifying Potential Carcinogens and Estimating Their Risks.

Table II-2a. Diallate IBT Studies

Type of Study	IBT No.	Status	Remarks
Fish & Wildlife			
8-Day LC_{50} Mallard Duck	651-3026	Valid	
8-Day Dietary LC_{50} Bobwhite Quail	J-6672	Valid	
8-Day Dietary LC_{50} Bobwhite Quail	J-6673	Valid	
8-Day Dietary LC_{50} Bobwhite Quail	651-3025	Valid	
4-Day Fish Tox	665-3027	Valid	
Fish & Wildlife	A-6675	Invalid	No raw data
Fish & Wildlife	A-6674	Invalid	No raw data
Fish & Wildlife	A-6849	Invalid	No raw data
Acute Studies			
4-week Pilot oral study	8531-9714	Valid	
Pilot feeding study/mice	8532-9820	Invalid	Incomplete raw data
Acute Inhalation	59-13-3	Invalid	No raw data
Acute cholinesterase	8530-9030	Valid	

Table II-2a. (continued). Diallate IBT Studies

Type of Study	IBT No.	Status	Remarks
Subacute Studies			
Subchronic oral	59-13A	Invalid	No raw data
Subchronic oral	59-13-2	Invalid	No raw data
Subchronic oral	59-13	Invalid	No raw data
Subchronic oral	59-13-1	Invalid	No raw data
Chronic Studies			
Teratogenicity/rabbits	651-5254	Invalid	Deficiencies in experimental design
Mutagenicity/mice	622-5252	Invalid	No raw data
Neurotoxicity/chicken	8580-9119	Valid	
Neurotoxicity/chicken	8580-10813	Invalid	No raw data
Chronic feeding/rats	622-5250	Invalid	Incomplete raw data

TDAP Evaluation of IBT Rat Study

The IBT study sumitted by Monsanto was evaluated by the Office of Pesticide Program's Toxicology Data Audit Program (TDAP). The analysis of the study indicates that the 2-year feeding study is invalid because of the lack of histopathology data, food consumption data, organ weight data on surviving animals, and dietary preparation data to show unequivocally that doses were correctly prepared. Therefore, no scientific conclusions can be drawn from this study.

a. Errors in Tabulated Data

Monsanto observed errors in the data cited in the CAG report and in their rebuttal submitted a retabulation of the raw data. Monsanto contended there are no statistically significant differences in the number of animals with tumors in the diallate-treated groups as compared to the controls (Monsanto Co., #1A[30000/15]).

The CAG has re-evaluated the raw data and has corrected its report accordingly. The revised CAG tabulation (shown in Tables II-3 and II-4) now agrees with the retabulation submitted by Monsanto Company. The data indicate that there is no statistically significant increase either of total tumors (benign and malignant) or of tumors of any anatomical site in any diallate-treated group of male rats as compared to controls.

As Table II-5 indicates, however, female rats treated with 100 ppm diallate (middle dose) showed a statistically significant increase of benign mammary tumors ($p = .021$) and hence of total mammary gland tumors (Albert, 1979). Therefore, the last portion of this rebuttal is rejected.

b. No Statistical Increase in Mammary Tumors

The incidence of mammary tumors in diallate-treated female rats is shown in Table II-5. Monsanto Company pointed out that there was no statistically significant increase in the number of mammary tumors in the treated female rats of the high- or low-dose groups as compared to the controls. The respondent argued that the admittedly statistically significant increase in mammary tumor among the middle-dose groups represents a random event, since there was no dose response. Monsanto pointed out further that there is no statistically significant increase of mammary carcinomas. (Monsanto Co., #1A[30000/15])

As Monsanto noted, the female rats of the middle dose group exhibited a statistically significant increase of total mammary tumors ($p = .021$), which was attributable to the statistically significant increase in benign mammary tumors ($p = .021$). This increase of benign mammary tumors in the middle-dose group may indicate an adverse effect, although the possibility that this response may be a random event cannot be

Table II-3. IBT Rat Study, Incidence of Benign and Malignant Tumors in Male Rats Ingesting Diallate[a/] [b/]

Dose Group	No. of Rats with Benign Tumors	No. of Rats with Malignant Tumors[a/] [c/]	Total No. of Rats with Tumors
Control	1/50 (2%)	4/50 (8%)	5/50 (10%)
50	0/50 (0%)	7/50 (14%)	7/50 (14%)
100	2/49 (4%)	4/49 (8%)	6/49 (12%)
200	1/50 (2%)	6/50 (12%)	7/50 (14%)

[a/] Revised CAG tabulation (Albert, 1979a).
[b/] Rats with endocrine tumors are not included.
[c/] Rats with both benign and malignant tumors were tabulated as having malignant tumors.

Table II-4. IBT Rat Study, Incidence of Carcinomas and Sarcomas in Male Rats Ingesting Diallate[a/][b/][c/]

Dose Group	No. of Rats with Carcinomas	No. of Rats with Sarcomas[a/]	Total No. of Rats with Malignant Tumors[d/]
Control	0/50 (0%)	4/50 (8%)	4/50 (8%)
50	3/50 (6%)	4/50 (8%)	7/50 (14%)
100	1/49 (2%)	3/49 (6%)[e/]	4/49 (8%)
200	2/50 (4%)	4/50 (8%)	6/50 (12%)

[a/] Revised CAG tabulation (Albert, 1979a).

[b/] Table II-4 is an elaboration of Total Malignant Tumors column in Table II-3.

[c/] Rats with endocrine tumors are not included.

[d/] Rats with both benign and malignant tumors were tabulated as having malignant tumors.

[e/] One rat had metastatic fibrosarcoma to the lung and liver, another to the lung. No primary sarcomas were found in the two rats.

unequivocally refuted (Albert, 1979a). However, the high percentage of test animals with tumors in the high dose group strongly suggests that there is an adverse effect.

c. Spontaneous Pituitary Adenomas

Monsanto Company pointed out that there is a high spontaneous incidence of pituitary adenomas in the IBT rat study. The respondent pointed out further that there is no apparent significant increase in the incidence of this tumor in any treated group, nor any linear increase by dose observed (Monsanto Co., #1A[30000/15]).

The Agency agrees with this conclusion (Albert, 1979).

3. Rebuttal Pertaining to the NCI Mouse Study (Innes Study)

a. Study Invalid

Monsanto Company claimed that the Innes study is invalid for the following two reasons:

1) Only one dose level, the maximum tolerated dose (MTD), was used in the study. The rebuttal contended that the MTD has been redefined, thereby making the doses used in the study higher than what is now considered the MTD and invalidating the experiment.

2) The experimental design necessitated the dosing of litter-mates. The rebuttal contended that biological and statistical significance cannot be drawn from this inferior experimental design. Monsanto suggested that a bias of inherited tendencies (e.g., predisposition to hepatoma formation) cannot be eliminated because the litter mates were not randomly distributed among the test groups (Monsanto Co., #1A[30000/15).

The Agency rejects this rebuttal argument. Concerning Monsanto's point 1) above, the Agency points out that the MTD is defined in the NCI Guidelines as "...the highest dose of the test agent given during the chronic study that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity."[4/]

Innes et al. reported that the MTD was selected on the basis of a series of studies in which the maximal level given in a single dose, in 6 daily and in 19 daily doses, resulted in zero mortality.[5/]

4/ NCI Guidelines for Carcinogen Bioassay in Small Rodents, NCI Tech. Report Ser. No. 1, Feb., 1976, p. 14. U.S. Dept. of Health, Education and Welfare, PHS, NIH, NCI-CG-TR-1.

5/ Innes, J.R.M. et al (1969) Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note. J. Nat. Cancer Inst. Vol. 42, p. 1102.

Table II-5. IBT Rat Study, Incidence of Benign and Malignant Tumors of the Mammary Gland in Female Rats Ingesting Diallate[a/]

Dose Group (ppm)	No. of Rats with Benign Tumors[b/]	No. of Rats with Malignant Tumors	Total No. of Rats with Tumors
Control	14/50 (28%)	5/50 (10%)	19/50 (38%)
50	19/49 (39%)	4/49 (8%)	23/49 (47%)
100	24/48 (50%)	5/48 (10%)	29/48 (60%)[c/]
200	15/46 (33%)	10/46 (22%)	25/46 (54%)

[a/] Revised CAG tabulation (Albert, 1979a).

[b/] Rats with both benign and malignant tumors were counted as malignant.

[c/] The tumor incidence in the 100 ppm dose group compared to the control group is statistically significant ($p = .021$) (Fisher Exact Test).

A comparison of the survival data in the carcinogenicity study indicates that the number of 18-month survivors in the diallate-treated groups was similar to that of the vehicle (0.5% gelatin) and untreated control groups for each respective species/sex. Hence the doses given in the study were tolerated by the treated animals and therefore did not exceed the MTD.

In reference to Monsanto's point 2) above, Innes administered diallate to mice (in 0.5% gelatin) by stomach tube from 7 days to 4 weeks of age. Thereafter, the mice were weaned and were given diallate (without a vehicle) in the diet. Since the study began prior to weaning, each test group (e.g., diallate-treated, positive or negative control group) was comprised of litter-mates instead of a random assortment of litter-mates, which was precluded by the study design.

During the MRAK Commission review of this study, which recommended that human exposure to diallate be minimized,[6/] Mr. Carrol Weil presented a dissenting opinion which included criticism of the non-random allocation of animals. Monsanto cited Mr. Weil's criticism in its rebuttal.

In response to Mr. Weil's criticism on non-randomization, the MRAK Commission reported that "...the data were reexamined on a litter basis, in keeping with the Epstein-Mantel approach, rather than on the single-animals basis employed in the Journal of the National Cancer Institute report. All compounds which had been judged positive for tumor induction (significant at the 0.01 level, or stronger), remained positive."[7/] Thus, although non-randomization of litter-mates is not the optimal experiment design, there is no evidence in this study that a bias existed for a genetic predisposition to tumor occurrence (Albert, 1979a).

b. Sex Specificity--Increased Hepatomas in Male Mice

Monsanto Company acknowledged the statistically significant increase in hepatomas in male mice in the Innes study, but contended that the apparent sex-specificity is unusual (Monsanto Co., # 1A[30000/15]).

The Agency rejects this rebuttal point. The data from the Innes study indicate a statistically significant increase in hepatomas in both strains of male mice when compared with either their respective matched (vehicle) control, negative control, or pooled negative control

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6/ Report of the Secretary's Commission of Pesticides and Their Relationship to Environmental Health, Parts I and II. U.S. Dept. of Health, Education and Welfare, Washington, D.C. (1969), p. 470.

7/ Ibid p. 483.

groups; and a statistically significant incidence in female mice of strain X when compared with the pooled negative control group only. Contrary to Monsanto's assertion, hepatic tumors are known to occur more frequently in male mice than in females.[8/] (Albert, 1979a).

c. No Statistically Significant Increase in Pulmonary Adenomas

Monsanto Company argued that there was no statistically significant increase in pulmonary adenomas in either sex of either strain of mouse, whereas the CAG report indicated a small statistically significant increase of lung adenomas in both sexes of strain X and in males of strain Y (Monsanto Co., #1A[30000/15]).

The Agency rejects this point of rebuttal. Having re-analyzed the data, the CAG finds a borderline statistically significant increase of pulmonary adenomas in the diallate-treated males of strain X as compared with the matched (vehicle) control group ($p = .051$) and with the pooled control groups ($p = .041$). (See Table II-6) (Albert, 1979a).

B. Analysis of Data Submitted Since PD 1 for Other Possible Adverse Effects

1. Mutagenicity

In PD 1 the Agency, based on the two available studies, stated that it had insufficient data to indicate diallate is mutagenic. The two studies were one, an Ames test in bacteria, and the second, a dominant lethal study in mice (Keplinger 1974). On the basis of this conclusion, the Agency requested comments and information on diallate's mutagenic potential. Additional studies were submitted and evaluated, and the Agency now concludes that diallate meets the criteria stated in 40 CFR 162.11 for mutagenicity by multi-test evidence. The additional studies which led to the Agency's finding are discussed below.

In response to the Agency's request for additional information with regard to the possible mutagenic properties of diallate, Rinkus and Legator (1977) submitted a study entitled "Mutagenicity of Diallate." This study, an Ames test, investigated the mutagenic effects of diallate in five strains of Salmonella. Diallate exhibited mutagenic activity in strains TA 1535 and TA 100 which exceeded the mutation frequency of controls by factors of approximately 20 and 12 respectively. This activity was only observed in the presence of a microsomal activation system. No activity was observed in strains TA 1537, TA 1538, and TA 98 in identical tests.

8/ Stewart, H. L. (1976). Comparative aspects of certain cancers. Chpt. 10 in Cancer, A Comprehensive Treatise, Vol. 4, F. F. Becker (ed.), Plenum Press, New York.

Table II-6. NCI Mouse Study (Innes Study): Lung Tumors in Mice Ingesting Avadex (Diallate)

	Dose Group	Strain X		Strain Y	
		Male	Female	Male	Female
Pulmonary Adenoma	Matched Control	0/16*(0%)	0/16 (0%)	2/18 (11%)	1/17(5%)
Pulmonary Carcinoma		0/16 (0%)	0/16 (0%)	0/18 (0%)	0/17(0%)
Pulmonary Adenoma	Negative Control	2/17 (12%)	1/18 (5%)	2/18 (11%)	0/17(0%)
Pulmonary Carcinoma		0/17 (0%)	0/18 (0%)	0/18 (0%)	0/17(0%)
Pulmonary Adenoma	Pooled Control	5/79**(6%)	3/87 (3%)	10/90(11%)	3/82(4%)
Pulmonary Carcinoma		0/79 (0%)	0/87 (0%)	0/90 (0%)	0/82(0%)
Pulmonary Adenoma	560 ppm	4/16 (25%)	2/16 (13%)	4/18 (22%)	1/15(7%)
Pulmonary Carcinoma		0/16 (0%)	0/16 (0%0	0/18 (0%)	0/15(0%)

* p = .051 (Fisher Exact Test) for the incidence of pulmonary adenomas in the treated group compared with the matched control.

** p = .041 (Fisher Exact Test) for the incidence of pulmonary adenomas in the treated group compared with the pooled control.

In PD 1 an unevaluated study by Sikka and Florczyk (1978) was mentioned. The study investigated the ability of diallate to induce mutations in four strains of Salmonella typhimurium (TA 100, TA 1535, TA 98, and TA 1538) with and without a rat-liver microsomal activation system. The study has now been evaluated and found to show activity at the 1 ug per plate level in the TA 100 and TA I535 strains indicating base-pair substitutions with metabolic activation. Diallate did not cause mutation in strains TA 98 and TA 1538 (frameshift mutants). These results confirm the findings of Rinkus and Legator.

Litton Bionetics, Inc. (LBI) (Brusick, 1977b) investigated the effects of diallate in the L5178Y mouse lymphoma cell. The study concluded that "The test compound, CP 15336, induced forward mutation at the TK locus in L5178Y mouse lymphoma cells in the presence of an uninduced mouse liver S-9 metabolic activation system." No dose-related effects were observed in the absence of metabolic activation.

Studies by SRI International (Simon, 1978) for EPA show that diallate does not induce gene mutation in E. coli (WP2). The bioassay was designed to monitor induced genetic alteration in E. coli at the tryptophan locus. However, tests in E. coli are not as sensitive as tests in Salmonella and, therefore, positive findings may not be manifested through experiments in this organism (Sandhu, 1978).

Diallate's potential to cause primary DNA damage was studied in two strains of Saccharomyces cerevisiae. SRI International (Simon, 1978) employed strain D_3 to measure induced mitotic recombination and LBI (Brusick, 1977a) used strain D_4 to measure gene conversion. While positive results were reported for mitotic recombinations in the SRI study, the LBI study results were negative. However, this mixed finding does not detract from the finding of induction of mitotic aberrations, a supportive finding for mutagenesis.

Monsanto submitted a dominant lethal study in mice in 1975 (Keplinger, 1974). This study done by IBT was reported by Monsanto as a negative study. The TDAP program reviewed this study and found it to be invalid because of the lack of raw data.

2. Neurotoxicity

The Agency concluded in the PD 1 that diallate is neurotoxic at the dose levels tested. This conclusion was based on an IBT study in chickens (Keplinger, 1976b). That study did not provide a dose-response relationship nor a no observable effect level which is needed to determine a margin of safety.

In the diallate PD 1, published on May 31, 1977, registrants were given 180 days to complete appropriate neurotoxicity studies and submit the results to the Agency or face possible cancellation under the provisions of FIFRA Section 6(b)(1)[9/]. Monsanto submitted an

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9/ In 1978 FIFRA was amended to provide for suspension under Section 3(c)(2)(B).

IBT study in which diallate was administered to chickens[10/] at dose levels ranging from 0.01 to 0.32 gm/kg which were administered twice daily for 3 consecutive days (Phillips, 1977). Twenty days following the initial dose, all surviving birds were again given the same dose regimen. Controls were dosed with 0.32 gm/kg corn oil and positive controls received 500 mg/kg TOCP on day 0.

All positive controls exhibited lesions typically associated with delayed neurotoxicity (Phillips, 1977). No such lesions were found in the negative controls.

Two test birds, one in the 0.04 gm/kg and one in the 0.16 gm/kg group showed focal lesions of axonal degeneration and secondary demyelination in the sciatic nerve. While these lesions were described as morphologically indistinguishable from those observed in the positive control birds, the affected birds showed no clinical signs which could be characterized as delayed neurotoxicity prior to sacrifice. No dose response relationship was established nor were there any reasons given for the absence of lesions at the highest dose.

Both of these IBT studies were reviewed by the TDAP. The original study, discussed in PD1, was validated and therefore does demonstrate that diallate given at 312 mg/kg causes neurotoxic effects. However, as stated in PD 1, this study does not show any dose response with which to determine ultimate safety. The second IBT study on neurotoxicity was declared invalid. TDAP found that raw data were totally missing on this experiment.

The Agency's concerns on neurotoxic effects of diallate have not been addressed by the registrant. While attempting to satisfy the needs of EPA, Monsanto has failed to take adequate precautions to insure validity of their data. Therefore, although the Agency does not have enough data to quantify the potential neurotoxic risks of diallate, it has calculated the annual applicator exposure. The Agency has determined that the effect level is 600 times greater than the exposure level.

3. Reproductive Effects

Prior to the RPAR review the Agency requested Monsanto to perform a 3-generation reproduction study in rats. However, no time limit was imposed on the registrant. At the time of PD 1 only the data in the F^0 (parental) generation had been submitted. The final report is expected in 1980. This study will be evaluated by the Agency and its results will be included in PD 4.

10/ The study used 5 birds per dose group with dose given at 0.01, 0.02, 0.04, 0.08, 0.16, and 0.32 gm/kg.

C. Exposure Analysis

The Agency analyzes exposure to a pesticide as part of the overall risk assessment. The complete exposure analysis includes incremental exposures to various populations depending on the route of exposure (e.g. dietary exposure to the general population, occupational exposure to applicators, drift to farm families, etc.). In compiling the analysis, the Agency takes into account the use patterns and methods of application so all populations likely to receive exposure are included in the analysis.

1. Spray Applicator Exposure

a. Spray Applicators

Information concerning spray applicator exposure was provided by the Environmental Fate Branch of the Agency's Hazard Evaluation Division (HED) (Selim, 1978). Diallate is applied primarily as an emulsifiable concentrate with ground equipment by boom sprayer. Spray applicators are exposed to diallate by 1) dermal exposure during the loading of the sprayer and during the application process, and 2) inhalation of the volatilized compound.

Exposure from diallate has not been measured, consequently the Agency used published data on triallate to prepare exposure analysis for diallate (the mode of application and chemical-physical properties of triallate are similar to diallate). To further check these results, the Agency validated the assumptions used for diallate by an exposure analysis which was published for paraquat. The pattern of exposure to paraquat is similar for the applicator working with diallate. Therefore, the Agency felt justified in utilizing the paraquat data for extrapolation to diallate. Both of these extrapolations produced very similar results.

The estimated dosages were reported in mg/hr, then converted to mg/kg/year. The conversion from dermal exposure expressed in mg/kg/year to equivalent lifetime dietary exposure expressed in ppm in the diet is as follows:

$$X = \frac{60 \text{ kg (worker dermal exposure in mg/kg/yr) x 40 yr}}{365 \text{ d/yr } \underline{x}_2 70 \text{ yr x } 1.5 \text{ kg/d}}$$

$$= 6.26 \times 10^{-2} \text{ x (worker dermal exposure in mg/kg/yr)}$$

$$= \text{lifetime dietary exposure in ppm}$$

where X is ppm in diet, 60 is average body weight in kg, and 1.5 kg is the average daily dietary intake. A 40-year working history and a 70-year lifetime is assumed for the applicators. This value (X) will be used to calculate lifetime probability in the Risk Assessment Section (II.D.1).

Table II-7 presents data on the absorbed dose in mg/kg/year and parts per million for spray applicators exposed to diallate. Rubber gloves and coveralls were considered as protective clothing when calculating the exposure reduction levels.

The annual exposure to applicators of diallate is 0.516 mg/kg/yr (.0323 ppm) and 0.018 mg/kg/yr (0.0011 ppm) from dermal and inhalation exposure respectively (Selim, 1978). These estimates are based on 10% absorption from both routes (Gardner, 1980). Based on the assumption that dermal exposure would be reduced by a factor of 4 if protective clothning is used, the dermal exposure level can be reduced to 0.13 mg/kg/yr (8.1×10^{-3} ppm) (Selim, 1978).

b. Granular Applicators

An applicator's exposure from granular diallate applications would be lower than an applicator's exposure using the emulsifiable concentrate formulations. With the granular formulation there is no chance of exposure from spray drift or from spray splash as there is with the emulsifiable concentrate formulations. The granules do not adhere to the skin as the emulsifiable concentrates would. Additionally, because diallate is applied during the late fall or early spring in the northwestern states, it is likely that most diallate applicators would be wearing clothing such as long sleeved shirts and trousers to protect themselves from the cold as well as protect themselves against the diallate. However, for the brief period of loading the (pre-mixed) granular diallate formulations there is a potential dermal and inhalation exposure hazard to the applicator due to dust from the granules. To mitigate this potential hazard, the Agency suggests the use of rubber gloves and cloth face masks for applicators during the loading process.

2. Dietary Exposure

The human population encounters direct dietary exposure to diallate residues through consumption of the following foods: barley, lentils, peas, soybeans, sugar beets, corn (grain), and flax (seed).

Maximum worst-case exposure was developed from tolerances established for residues of diallate in foods. The FDA, in its Market Basket Survey, has not analyzed raw agricultural commodities specifically for diallate. It is assumed that residues are present in all individual raw agricultural commodities to the extent permitted by the tolerances and that the commodities are uniformly distributed throughout the country. Table II-8 presents the dietary exposure of the entire U.S. population to diallate.

A second set of estimates were developed which were based on available information concerning the percentage of crops treated and were provided by the Agency's Benefits and Field Studies Division (Lewis, 1978). Table II-8 presents the exposure estimates when the percentage of crop treated is considered.

D. Risk Assessment

1. Oncogenic Effects

The cancer risk assessment of diallate is based on the principles and procedures outlined in the EPA interim cancer risk assessment guidelines (41 FR 21402, May 25, 1976). These guidelines specify that a substance will be considered a "presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals." Current and anticipated exposure levels are appropriate considerations for establishing cancer risk estimates. These estimates may be derived from a variety of risk extrapolation models such as the log-probit and linear non-threshold models.

Table II-7 Diallate Dermal and Inhalation Exposure to Spray Applicators and Equivalent Lifetime Dietary Exposure

Route of Exposure	Estimated Dose mg/hr	Duration of Exposure	Dose in mg/kg/yr	Dose in ppm
DERMAL				
Absence of protective clothing (Assuming 10% dermal absorption)[1/]	2.58	6-12 hr/yr.	.258 .516	2×10^{-2} 3×10^{-2}
With protective clothing (Assuming 10% dermal absorption)[1/2/]	.65	6-12 hr/yr.	0.065 .13	4×10^{-3} 8×10^{-3}
INHALATION				
Without mask	.09	6-12 hr/yr.	.009 .018	6×10^{-4} 1×10^{-3}
With mask (10% of exposure without mask)	.009	6-12 hr/yr.	.0009 .0018	6×10^{-5} 1×10^{-4}

1/ 10% absorption is assumed in absence of data on diallate (Gardner, 1980).

2/ Assuming that protective clothing provides a four fold reduction in exposure. (Selim, 1978)

Table II-8. Annual U.S. Population Dietary Exposure to Diallate, Based On Tolerance Levels and Percent of Crop Treated

Source	Exposure Based on 100% of Crop Treated with Residues at Tolerance Levels ppm	Percent of Crop Treated with Diallate	Exposure Based on Actual Percent of Crop Treated with Residues at Tolerance Levels ppm
Barley	0.000013	0.10	0.00000
Lentils	0.00002	38	0.00001
Peas	0.00035	10	0.00005
Potatoes	0.00271	0.46	0.00002
Safflower*	0.000013	100	0.00002
Soybeans	0.00046	0.20	0.00000
Sugar beets	0.00001	14.3	0.00012
Corn, grain	0.0005	0.009	0.00000 **
Flax, seed	0.000013	3	0.00000 **
Total	0.004089		0.00022

* 100% is assumed in the absence of data

** Not actually "0", remaining significant figures truncated.

In accordance with these principles, the EPA Cancer Assessment Group (CAG) (Albert, 1979b) developed risk estimates based on several different models and a range of exposure estimates. After reviewing the data sources and the preliminary risk estimates, the CAG concurred in recommendations that the final quantitative risk estimates be based on data from the NCI mouse study (Innes study) using the one-hit model. The CAG used the Innes data because animals in the Innes study were fed the compound beginning at a younger age than were animals in the NCI (rat) or IBT studies, and therefore provided the most sensitive animal upon which to base the conservative analysis.

To develop a risk estimate, CAG evaluated the animal test data and the human exposure data using several different models. They selected the one-hit model because it provided the most conservative estimate of potential risk to humans.

As explained above, the animal bioassay data used for the quantitative risk assessment were based on the Innes oral feeding study in mice. In this study one treated group of mice were fed 560 ppm diallate in the diet. A statistically significant higher incidence of hepatomas in males of both strains X and Y was observed, as compared to matched controls (see Table II-9).

The proportion of hepatomas observed in Strain X males was used to calculate the slope parameter for the one-hit model, adjusting for background tumor incidence. Therefore, using the proportion of hepatomas in the matched control group and the treated group, the one-hit slope parameter is as follows:[11/]

$$B = \cdot \ln [(1-Pt)/(1-Pc)] /y$$

$$B = - \ln [(1- 13/16)/(1-0/16)]/570$$

$$= 2.989. \times 10^{-3}$$

From the slope, the estimate lifetime probability can be estimated from the following equation.

$$P = BX = (2.989 \times 10^{-3})X$$

(where X is the ppm in the diet from actual exposure and from equivalent dermal exposure as calculated in Section II.C.1.)

11/ Where: B = slope coefficient of the one-hit model
P = (Pt-Pc)(1-Pc)
Pc = Incidence of hepatomas in control animals
Pt = Incidence of hepatomas in test animals
Y = Test animal exposure (ppm)
x = Potential human exposure (ppm)

Table II-9. NCI Mouse Study (Innes Study): Liver Tumors (Hepatomas) in Mice Ingesting Diallate

Dose Group	Strain X		Strain Y	
	Male	Female	Male	Female
Matched Control (vehicle)	0/16*	0/16	1/18*	0/17
Negative Control	1/17*	0/18	3/18**	0/17
Pooled Control	8/79*	0/87**	5/90*	1/82
560 ppm	13/16	2/16	10/18	1/15

* Statistically significant when p is $\leq$ .01.
** Statistically significant when p is $\leq$ .05.

The exposure estimates for dietary and applicator exposure were factored into the above equation. Risks from these exposures are shown in Tables II-10 and II-11. A dietary worst-case risk of 10^{-5} occurs at tolerance levels assuming that 100% of the crops are treated. It is not likely that 100% of the crops will be treated with diallate. Therefore using the projected percentages of treated crops from Section III, results in a reasonable worse case risk of 10^{-7}.

Risk to applicators without protective clothing is estimated at 10^{-4}, a relatively high risk. With protective clothing, risk to applicators is improved to 10^{-5} (Table II-11).

Aggregated, these risks imply that 1 in 10,000 applicators might have a lifetime risk of developing a diallate induced tumor taking into account both occupational and dietary exposure. It is estimated that there are 2380 diallate applicators (Selim, 1978). The general population would have a lesser risk (10-7), but this is based on current usage and should any increase in usage occur, the dietary risks would increase.

2. Mutagenic Effects

While adequate evidence exists to establish the mutagenicity of diallate in in vitro systems, no quantitative assessment of risk can be made because of (1) insufficient data from mammalian test systems(Mauer, 1978), and (2) no generally applicable method has been developed to quantify mutagenic risk.[12/] Recent studies have established a strong correlation between a chemical's carcinogenic potential and its ability to induce mitotic recombination (Sandhu, 1978).

12/ The Agency has not yet developed a standard procedure for defining mutagenic risk in quantitative terms. At the present time, much attention is being focused on developing a battery of test systems and other data that are predictive of mutagenic risk in humans. Until such time as more quantitative methods and procedures for risk estimation are developed for each mutagenic endpoint of concern, the Agency will evaluate each mutagenic chemical on a case-by-case basis, taking into account all available test data. The approach taken by the Agency will of necessity be conservative in order to assure that man and the environment are protected from the risk of "unreasonable adverse effects" through the action of mutagenic agents. The evolving nature of methodology in the field of mutagenicity testing dictates that the Agency will revise its risk estimation procedure for future chemicals under evaluation as superior risk predictive models and other relevant information become available. As well, the Agency will revise its risk estimates for chemicals which have previously been subjected to risk assessments if additional more relevant test data and other predictive information are developed.

Table II-10. Lifetime Spray Applicator Cancer Risk from Dermal and Inhalation Exposure to Diallate

Route	Equivalent Lifetime Dietary Dose Assuming 12 Hour Annual Exposure (ppm)	Lifetime Probability of Cancer Due to Diallate
DERMAL		
Without protective clothing*	3×10^{-2}	1×10^{-4}
With protective clothing (10% absorption)*	8×10^{-3}	2×10^{-5}
INHALATION		
Without mask	1×10^{-3}	3×10^{-6}
With mask (10% of exposure without mask)*	1×10^{-4}	3×10^{-7}

* 10% absorption is assumed in the absence of data on diallate (Gardner 1980).

Table II-11. Cancer Risk to U.S. Population from Dietary Exposure to Diallate

Source	Lifetime Probability of Cancer Based on 100% of Crop Treated Residues at Tolerance Levels	Lifetime Probability of Cancer Based on Estimated Percent of Crop Treated with Residues at Tolerance Levels
Barley	4×10^{-8}	4×10^{-11}
Lentils	6×10^{-8}	2×10^{-8}
Peas	1×10^{-6}	1×10^{-7}
Potatoes	8×10^{-6}	4×10^{-8}
Safflower	4×10^{-8}	4×10^{-8}
Soybeans	1×10^{-6}	3×10^{-9}
Flax seed	4.9×10^{-6}	Negligible
Beet Sugar	1×10^{-6}	2×10^{-7}
Corn	1×10^{-6}	Negligible
Total	1×10^{-5}	4×10^{-7}

E. Risks Associated with Alternative Chemicals

Several chemicals have been proposed as alternatives should diallate become unavailable. In non-irrigated areas, eptam would be the major substitute with barban and dalapon used to a lesser extent. In irrigated areas cycloate and barban are the major substitutes. Eptam and barban are substitutes used on flax. Triallate, propham and barban are alternative chemicals for use on lentils and peas.

The data bases for the alternative chemicals are not complete. A complete list indicating the studies which the Agency has on hand appears in Table II-12. Based on the studies reviewed for all alternatives other than triallate, no unreasonable adverse effects were found associated with the proposed alternatives. Because of the lack of chronic studies no qualitative ranking of alternatives can be made with regard to their relative toxicities.

The battery of toxicological tests performed on triallate include mutagenic, chronic feeding, teratogenic, and neurotoxic studies. Triallate was found to exhibit mutagenic activity in the Ames test in bacteria with metabolic activation. It was also found to be positive in yeast when tested for mitotic recombination. Negative findings were reported to gene conversion in yeast, mouse lymphoma, and dominant lethal assays. When triallate is compared to diallate in tests which are positive for both, diallate is at least 3 times more active.

Negative findings for triallate were reported in a chronic feeding study in rats. This study was evaluated by TDAP and found to be valid only as an oncogenic screen test because of deficiences in the experimental design.

The teratogenic and neurotoxic studies on triallate were performed by IBT. These studies were evaluated by TDAP and found to be invalid.

Table II-12 TOXICOLOGICAL DATA SUMMARY FOR DIALLATE ALTERNATIVES (CHRONIC DATA)

CHEMICAL	ONCOGENICITY	MUTAGENICITY	CHRONIC FEEDING	TERATOGENICITY	REPRODUCTIVE EFFECTS	NEUROTOXICITY
Triallate	**Rat	Gene Conversion (-) Mitotic Recombination (+) Bacteria 4+ (with activation) 2- (no activation) Dominant Lethal (-) Mouse Lymphoma (-)	**Rat (-)	Rabbit (Invalid)	N/A	Chicken (2 Invalid Studies)
Barban	N/A	N/A	Dog (-)	N/A	N/A	N/A
Cycloate	N/A	N/A	Rat (-)	N/A	N/A	N/A
Dalapon	N/A	N/A	Rat (-)	Dog (-) Rat (-)	N/A	N/A
EPTC* (Eptam)	No Data Available					

(+) Positive Study
(-) Negative Study
* EPTC has negligible residue tolerances, therefore no chronic data have been submitted.
** This IBT study listed under "Oncogenicity" and "Chronic Feeding," was reviewed by TDAP. While the study was considered invalid as a chronic feeding study, it was found valid as an oncogenic screening study.

III. Benefit Analysis

As a pre-emergence selective herbicide, diallate is used as a soil treatment on field crops for control of wild oats. Because Monsanto is the sole producer of diallate, production and marketing data are confidential. However, it is estimated that approximately 390,000 pounds active ingredient of diallate were applied annually to 319,000 acres of sugar beets, flax, lentils, and peas, the major use sites of diallate between 1976 and 1978. Small amounts of diallate are also applied to potatoes, soybeans, barley, corn, and forage legumes.[1/]

The Agency has received 16 submissions from registrants and interested parties pertaining to the benefits of diallate, in particular as it is used on sugar beets, lentils, and peas. The Agency considered this information in analyzing the benefits of diallate.

For sugar beets, flax, lentils, and peas, the estimates of acreage treated, the identification of biologically viable alternatives, and the use data were based primarily on Assessment of the Need for Diallate in Agriculture, USDA/State Assessment Team on Diallate (September, 1977, and 1979 modifications). The economic analysis based on these biological data was prepared by Development Planning and Research Associates, Inc. in March of 1979.

However, lack of published data on yield changes limited certain aspects of the analysis. Expert opinion was used in place of these data. Alternate weed control strategies also lacked firm data, necessitating the use of expert opinion to generate impacts of alternate control programs (USDA/State Assessment Team, 1977).

The alternatives to diallate were selected on the basis of cost, efficacy, and availability. Partial budgeting was employed to assess the economic impacts of diallate cancellation.[2/] The partial budgeting methodology allowed the change in the cost of weed control to be measured, together with the effect on gross returns associated with substituting alternative weed control practices while all other inputs were held constant. The economic analysis also assumed that in some instances the cancellation of diallate would cause growers to shift production to alternative crops. In these cases, net returns to the producer associated with the production of alternative crops were evaluated.

1/ The USDA/State Assessment Team on Diallate (August 31, 1977) estimated that approximately 10,000 acres or less of each of these crops were treated with diallate annually, accounting for 0.5% or less of the total crop planting in each case. The Monsanto submission filed September 9, 1977, did not address the benefits of diallate use on any of these minor crops.

2/ The partial budgeting methodology allows the measurement of the change in the cost of pest control and the effect on returns associated with substituting alternative chemical and non-chemical pest control practices into the budget with all other inputs held constant.

If the major uses of diallate on sugar beets, flax, peas, and lentils were cancelled, varied effects on producers would result. Because an acceptable substitute herbicide is available, peas and lentils would actually return more income to producers if diallate were cancelled. The positive economic impact is based on increased yields which are due to a decrease in phytotoxicity and better wild oat control in some instances, see further discussion in Section III.C. Sugar beet producers would suffer an estimated adverse impact of $4.0 million. Flax producers are expected to experience an estimated $0.4 million economic loss. The net adverse impact upon all affected user groups is approximately $3.2 million annually.[3/] These aggregate economic impacts are summarized in Table III-1. The following subsections (A through E) briefly explain the economic impacts involved should the major and minor uses of diallate be cancelled.

A. Sugar Beets

Sugar beet production subject to wild oat infestation is located in the non-irrigated acreage of Minnesota and North Dakota, and irrigated acreage in Montana, Wyoming, Idaho, Utah, Washington, Oregon, and California. As an average for the period 1976-1978, see Tables III-2 and III-3, these nine states planted 995,000 acres of sugar beets annually or 72.6% of the U.S. total acreage. Of the nine-state total, 418,000 acres, or 42%, were in Minnesota and North Dakota; 577,000 acres, or 58%, were in the seven western states subject to wild oat infestation.

Diallate is a major herbicide used to control wild oats in sugar beets. It is most widely used in non-irrigated acres. As an average during the 1976-1978 period, diallate was estimated to have been applied to 185,175 acres of non-irrigated beets, and to 35,800 acres of irrigated beets. In total, diallate was applied to 220,975 acres, or 22% of the total sugar beet acreage subject to wild oat infestation.

Annual use of diallate to control wild oats in sugar beets, as an average for the period 1976-1978, was estimated to have been 231,470 pounds (active ingredient basis) in non-irrigated areas and 44,750 pounds in irrigated areas. Total estimated use of diallate on sugar beets is thus 276,220 pounds.

Two formulations of diallate are used on sugar beets. Granular diallate is applied to approximately 15% of the treated acreage while the emulsifiable concentrate is applied to approximately 85% (Lewis, 1979). The degree control of wild oats provided by each of these formulations appears to be the same for the fall application. There is some decrease in control of wild oats when the granular is substituted for the emulsifiable concentrate in the spring application.

3/ This reflects an estimated 1.2 million net increase in revenues when triallate is substituted for diallate where it is also registered for these uses.

Table III-1. Annual Economic Impact of Cancellation of Diallate on the Major Use Sites [a/]

Site	Extent of Use (thousand pounds)	Units Treated (thousand acres)	Percent of Total Units	Aggregate Economic Impacts		Total Market Value (million dollars)
				User (million dollars)	Market & Consumer (million dollars) [b/]	
Sugar beets	276.2	221.0	16.7	4.0 loss	none	500
Flax	38.4	30.7	3.0	.4 loss	none	59
Lentils	43.3	43.3	38.0	.7 gain	none	34
Peas	30.4	24.3	10.5	.5 gain	none	23.6
Major use total	388.3	319.3	-----	3.2 net loss	-----	

[a/] Source: Economic Analysis of Effects of Restricting Use of Diallate on Sugar Beets, Flax, Lentils, and Dry Peas. Development Planning & Research Associates, Inc. March, 1979.

[b/] 1978 price levels

Table III-2. Estimated annual aggregate use costs for eliminating diallate on irrigated sugar beets, 1976-1978

	Acres*	Costs				Total costs
		Material	Application	Yield loss**	Other costs	
		($)	($)	($)	($)	($)
With diallate	35,800	225,540	125,658	---	---	351,198
Without diallate						
Cycloate	8,200	192,536	28,782	167,132		388,450
Propham	300	3,960	1,053	42,660		47,673
Dalapon	1,800	8,262	2,862	42,660		53,784
Barban	1,800	20,318	2,862	122,860		146,040
Paraquat	1,800	36,000	2,862	133,100		171,962
Untreated	5,600	---	---	665,350		665,350
Hand weeding a/	8,200	---	---	---	164,000	164,000
Added cultivation b/	10,700	---	---	129,418	27,713	157,131
Delayed seeding	900	---	---	42,660	---	42,660
Shift to other crops	6,400	---	---	---	1,652,000	1,652,000
Sub-total w/o diallate	45,700	261,076	38,421	1,345,840	1,843,713	3,489,040
Net change w/o diallate		35,536	(87,237)	1,345,840	1,843,713	3,137,852

* USDA/State Assessment Study, percentage of original acreage estimated to be treated with diallate.
** Loss per acre from USDA/State Assessment Study, 1977. Sugar beets valued at $23.70/ton.
a/ Charge at $20 per acre, based on interview information from sugar beet processors.
b/ North Dakota Crop and Livestock Reporting Service, 1977.

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Table III-1. Estimated annual aggregate user impacts for eliminating diallate on non-irrigated sugar beets.

Item	Acres	Costs			Total cost	Change in cost
		Material	Application	Yield loss		
		($)	($)	($)	($)	
Herbicide Effect	---	---	---	---		+ 116,292
a. with diallate	185,175	1,166,608	649,964	---	1,816,572	
b. diallate substitutes	---	---	---	---	1,932,864	
1. eptam	38,040	345,960	133,520	---	---	
2. tarban	97,270	1,104,068	154,659	---	---	
3. dalapon	25,565	152,419	42,238	---	---	
Cultural Effect	---	---	---	---		+ 321,847
a. with diallate	---	---	---	---	4,466,420	
1. seed	185,175	2,481,345	546,266	---	---	
2. cultivate (1x)	185,175	---	1,438,809	---	---	
b. without diallate	---	---	---	---	4,788,267	
1. seed	186,805	2,503,187	551,075	65,852*	---	
2. cultivate (1x)	185,175	---	1,438,809			
3. cultivate (4x)	88,550	---	224,344			
Hand labor	---	---	---	---		+ 430,126
a. with diallate	---	---	---	---	4,710,860	
1. thinning	74,070	---	1,917,672	---		
2. weeding (2x)	83,129	---	2,793,188	---		
b. without diallate	---	---	---	---	5,140,986	
1. thinning	74,070	---	2,051,739	---	---	
2. weeding (2x)	83,329	---	2,980,177	---	---	
3. extra weeding	2,215	---	101,070	---	---	

* Reduced yield of 2 ton/acre at $20.20 per ton (source of yield loss estimate, USDA/State Assessment Team, 1977)

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Should diallate use on sugar beets be cancelled, procedures will substitute an integrated chemical and cultural strategy for wild oat control. In non-irrigated areas, eptam is a major substitute for diallate, with barban and dalapon also used for wild oat control. In irrigated areas, cycloate and barban are the major substitute herbicides. Sugar beet producers would also need to increase the amount of mechanical and hand labor used to cultivate their beets. Some producers may experience yield losses with alternative weed control strategies (including use of alternative herbicides and delayed seeding), while other producers may shift to alternate crops.

Economic impacts would result from changes in herbicide costs, increased mechanical and hand cultivation costs, additional reseeding costs, decreased yields, and shifts to other crops. Should diallate be cancelled, sugar beet producers may experience estimated economic losses potentially as high as $4.0 million (Tables III-2 and III-3). Of that $4.0 million impact, approximately $3.1 million would result from adverse effects in the irrigated sugar beet areas of the Western U.S., and $0.9 million would be attributed to ramifications in the non-irrigated Red River Valley area of North Dakota and Minnesota. In the Red River Valley most of the adverse impact would derive from possible increased hand labor costs and possible increased mechanical cultivation costs. In irrigated areas, losses would be nearly equally divided between yield losses and lost revenue resulting from changes in crop production from sugar beets to other crops.

The effect of diallate cancellation on a typical Red River Valley farm with 185 acres of sugar beets would be increased costs of $870 annually. The average cost increase per acre of sugar beets is $4.69. This, of course, assumes the typical farm would make all herbicide, cultural, and labor adjustments in the same proportions as the entire Valley area. Changes in net yield are not anticipated. The average producer could expect his net returns to land, management, and labor to decrease by only 2.1%, from $41,102 to $40,232.

The effect of diallate cancellation on a typical irrigated sugar beet farm would be much more severe, with an average impact of $87.65 per acre of sugar beets. On a farm which ordinarily treated 100 acres of sugar beets with diallate, the adverse annual effects would amount to $8,765, most of which would be due to reductions in net returns (over variable cost). For a typical farm, crop returns over variable cost would be reduced nearly 18%. This loss, however, is to the individual farmer. There is little overall yield loss since diallate is not used extensively in irrigated plantings. In a switch to the granular formulation of diallate alone for the control of wild oats in sugar beets, the increased cost to growers in the short run will be approximately $6-$7 per acre treatment, given current prices.

While the cancellation of diallate may pose significant problems to the local grower, this effect will not seriously reduce total U.S.

production because the sugar from sugar beets represents only a small percentage of total U.S. sugar consumed. Over 50% of the U.S. sugar is now imported due to the favorable tariff for imports. A decline in profit because of sugar imports is already reducing sugar beet acreages.

B. Flax

United States flax production is concentrated in the states of Minnesota, North Dakota, and South Dakota. This area produced 98% of U.S. flax on an average of 1,025,000 acres between 1976 and 1978. Approximately 3% of the total flax acreage (30,750 acres) was estimated to have been treated with diallate during this period - an estimated 38,440 pounds (active ingredient basis) of diallate annually. The emulsifiable concentrate formulation is the only form of diallate currently registered for use on flax; however, granular diallate could be used on flax if it were registered, but at slightly higher costs. Herbicide use on flax is very limited because of the extreme phytotoxic reaction of flax to any herbicide, including diallate. Diallate is, however, used in preference to other herbicides.

Eptam and barban are the most common herbicides which can be substituted for diallate to control wild oats in flax; however, both of these chemicals have characteristics which limit their use on flax. Eptam is phytotoxic in flax, and barban can only be applied when the wild oats are at the two leaf stage (2-4 days). If weather is bad for that period the effectiveness of the chemical is lost. A cultural method of wild oat control is delayed seeding; however, this non-chemical method of weed control reduces flax yields by about 33%.

Cancelling the use of diallate on flax is anticipated to result in annual losses of approximately $0.4 million to flax producers. The economic impacts result from a combination of changes in herbicides costs, shifts in production from flax to alternative crops, and yield losses resulting from delayed seeding. The average loss in returns per acre of flax treated with diallate substitutes would be $13.59. This loss represents 25% of the expected returns to land, labor, and management with diallate available.

Since only 3% of the total flax acreage is estimated to be treated with diallate, the cancellation of diallate would not have a significant effect on total flaxseed supplies or established marketing systems or patterns. Moreover, some shift in production away from flax is already occurring because of decreasing demand for flaxseed and flax straw. (USDA, Crop Production Annual Summary, 1978.)

C. Lentils

Commercial lentil production is located almost entirely in Washington and Idaho. During the 1976-1978 period, an average of 114,000 acres of lentils were planted annually in these two states. Both states

are subject to wild oat infestations, and diallate is a major herbicide used to control wild oats in lentil plantings. It is estimated that 43,320 acres or 38% of the total lentil acreage were treated with diallate. With a normal use rate of one pound (active ingredient basis) of diallate applied per acre, this would require 43,320 pounds of diallate.

Use of triallate provides an excellent substitute for diallate use on lentils. Triallate, although increasing the overall costs of wild oat control, offers increased yields which more than offset the increase in costs. The positive economic impact is based on increased yields resulting from triallate being less phytotoxic and in some cases better control of the pest. Triallate would pick up an estimated 93% of the diallate usage if diallate were cancelled. Therefore, cancellation of diallate and a shift to triallate would have a positive impact to growers by increasing returns by $512,000 annually, with an increase in production of 1.6%.

The growers reluctance to switch to triallate may be 1) unfamiliarity with triallate, 2) inconvenience of stocking additional chemicals when diallate can treat all crops, and 3) marketing preferences.

Other herbicides which are expected to offset the impact of diallate's cancellation on lentils include propham and barban. However, these two herbicides are not as useful as triallate because of altered efficacy characteristics (e.g. critical timing for effectiveness and rapid biodegradation in soil). Therefore, these herbicides are not considered as complete alternatives for diallate.

D. Peas

Dry peas (including Austrian winter peas and wrinkled seed peas) are produced primarily in Washington and Idaho. During the 1976-1978 period, an average of 231,000 acres of dry peas were produced in these two states. Wild oats are a major pest in dry pea production. Approximately 11% of the total acreage is treated with diallate for wild oat control, using 30,375 pounds (active ingredient basis) of diallate.

Triallate is considered the primary substitute for diallate. Triallate is already used on 45% of the dry peas produced and offers growers a larger return on the land through increased yields (see discussion in III.C.), so that the total return to the grower increases by nearly $730,000 annually.

Propham and barban are also registered for use in dry peas. However, these two chemicals have limitations which preclude their total effectiveness as alternatives. Upon diallate's cancellation, the usage of both propham and barban would increase above the current 2% (propham) and 6% (barban) usage on dry peas.

The cancellation of diallate is anticipated to result in U.S. dry pea production increases of less than 0.01%. Therefore no economic impacts would occur at either the market or consumer levels.

E. Minor Uses

Diallate, in addition to the foregoing major uses, is also registered for use on soybeans, corn, barley, potatoes, safflower, and alfalfa. The percentage of use on each of the above crops is quite small; thus, use of diallate has been determined to be minor on these crops. Use of diallate on these crops is basically limited to North Dakota, Minnesota, Montana, and Idaho.

The estimated use of diallate on potatoes is 0.5% of the total potato acreage. For all other minor crops except safflower and alfalfa, the total treated acreage is thought to be 0.1% or less. Data are not available to show the total amount of diallate used on safflower and alfalfa acreage.

If diallate becomes unavailable, barban would be used to control wild oats on soybeans, and eptam would be the chemical of choice in corn and potatoes. Triallate is registered for use on barley. Monsanto has expressed a desire to register triallate for all crops for which diallate is now registered (Spurrier, 1979).

The cancellation of diallate on the crops discussed in this section is not expected to have any economic impact upon the grower or market prices. Only in the case of potatoes does the use approach 0.5% of the total acreage. In other cases, diallate treated acreage amounts to 0.1% or less of the total acreage.

IV. Development of Regulatory Options

A. Introduction

The risks and benefits associated with the uses of diallate have been identified in Sections II and III. As explained in Section I, FIFRA mandates that the Agency achieve a balance between the competing considerations of risks and benefits. In order to carry out that mandate, the Agency has developed various regulatory options and has evaluated each option for its impact on both sides of the risk/benefit equation.

This section of Position Document 2/3 briefly summarizes the salient risks and benefits associated with the uses of diallate and describes the process by which the Agency developed potential courses of action.

B. Salient Risk/Benefit Considerations

In performing a risk/benefit analysis of the uses of diallate, the Agency identified several salient factors, on both sides of the risk/benefit equation, which became determining considerations in the development of regulatory options. These considerations are reviewed below.

1. Salient Risk Considerations

As detailed in Section II of this document the original risk criteria cited in the RPAR notice as the basis for the Agency's presumption against diallate stands unrebutted. The principal risk associated with the use of diallate is oncogenicity. This risk manifests itself in the general population through dietary exposures at very low levels and to pesticide applicators through dermal and inhalation exposures when applying diallate as an emulsifiable concentrate.

It is estimated that there are approximately 2400 pesticide applicators currently at risk. This risk is estimated to be 10^{-4} and is of primary concern to the Agency (Table II-10). The dietary risk to the general population is estimated to be 10^{-7} based on tolerance levels adjusted to reflect the percent of crop treated (Table II-11). The Agency considers the dietary risks of diallate to be low and not of primary concern when compared to the benefits associated with its use.

Since the original RPAR notice was published the Agency received additional evidence to support the conclusion that diallate is a mutagen. Although quantitative estimates of the mutagenic risk to applicators are not possible at this time, any risk reduction procedures proposed to reduce the oncogenic risks of diallate will concomitantly reduce mutagenic risks.

There is also evidence that diallate causes neurotoxic effects. As in the case of mutagenic risks quantitative estimates of risk

are not presently possible. However, based on current exposure estimates there is a 600-fold span between the observed effect level and the exposure level.

2. Salient Benefit Considerations

The benefits of diallate were assessed in terms of the economic impacts which would result if its uses were cancelled and users were thereby forced to employ available alternatives. As detailed in Section III, the economic impacts associated with the cancellation of diallate total just over $3 million (Table III-1).

Sugar Beets

The total annual market value of sugar beets is $500 million. Should diallate become unavailable, growers are expected to experience an annual loss of $4 million. More than 60% of the diallate used in this country is applied to sugar beets. Presently the emulsifiable concentrate formulation is applied to 85% of the treated acreage while the granular formulation is applied to the remaining 15%. The degree control of wild oats provided by each of these formulations appears to be the same.

Several alternative chemicals were identified in Section III of this document. Specifically mentioned were, 1) cycloate for control in irrigated areas, and 2) eptam for control in non-irrigated areas, and 3) barban which can be used in both areas. However, due to certain limitations (see Section III.A) none of these chemicals provide adequate protection against wild oats.

In changing to granular diallate alone for control of wild oats in sugar beets, the increased cost to growers in the short run will be approximately $6-$7 per acre-treatment given current prices.

Flax

Approximately 3% of the total flax acreage is treated with diallate. If all forms of diallate should become unavailable for use in the control of wild oats in flax, growers are expected to experience a $400,000 annual loss. The emulsifiable concentrate is the only formulation presently registered for this use.

Eptam and barban are the most commonly used alternatives for diallate. Both of these chemicals have limitations which reduce their desirability and effectiveness in the control of wild oats (see Section III.B). Granular diallate is anticipated to provide effective control of wild oats in flax; however, this formulation is not currently registered for this use.

Lentils

Thirty-eight percent of the total lentil acreage is treated with diallate. Lentil production is basically limited to two western states, Idaho and Washington. It is estimated that more than 43,000 pounds of diallate are applied to lentil acreage annually. The emulsifiable concentrate is the only diallate formulation presently registered for this use.

The major alternate chemical used to control wild oats in lentils is triallate. Triallate has proven to be an effective alternate and provides control of wild oats equal to or greater than that provided by diallate. Triallate is also less phytotoxic to lentils than diallate. Propham and barban are alternative chemicals but do not provide acceptable control of wild oats.

Peas

Dry peas, like lentils, are primarily grown in Idaho and Washington. Currently, approximately 11% of the dry pea acreage is treated with diallate. Only the emulsifiable concentrate formulation of diallate is registered for use on peas for the control of wild oats.

Triallate is the primary alternate chemical for diallate on peas. Presently, triallate is used on 45% of the dry pea acreage. Triallate is less phytotoxic to peas than diallate.

Minor Uses (Alfalfa, Barley, Corn, Potatoes, Safflower, and Soybeans)

The total percent of minor crop acreage treated annually with diallate ranges from <0.1% to 0.5%. More specifically, it is estimated that 0.5% of the potato acreage is treated, whereas the percentage of treated acreage for all other crops is 0.1% or less. No economic impacts are expected if diallate is cancelled. Only the emulsifiable concentrate formulation is registered for the minor uses.

Barban and eptam are considered as possible substitute chemicals. Triallate is now registered for use on barley.

C. Risk/Benefit Analysis

1. Dietary Risk/Benefit Analysis

As indicated in Section II.D.1. the dietary risk from diallate is estimated as 10^{-7}. This estimate is based on assuming residues exist on treated crops at the tolerance level. This is a worst case assumption and to date, residues have not been found on any crops at the level of detection (.02 ppm). More than 60% of the dietary risk is attributable to the use of diallate on sugar beets. The dietary risk is

considered to be low and the benefits of diallate use are moderate for sugar beets and flax, and low for lentils, peas, and minor crops. In sugar beets the average cost increase per acre will range from $4.69 to $87.65. For flax the loss in returns per acre would be about $14. For all other uses economic benefits would accrue due to minor production increases from either more effective control of wild oats or decreased phytotoxic effects of alternate chemicals. Therefore, the Agency concludes that the benefits (low to moderate) outweigh the dietary risk (low). In view of this, regulatory action on the basis of dietary risk alone is not warranted. As indicated above the principal risk of diallate is to pesticide applicators through dermal and inhalation exposure when applying diallate as an emulsifiable concentrate.

2. Applicator Risk/Benefit Analysis

The applicator risk/benefit matrix for diallate, expressed in qualitative terms, is shown in Table IV-1. For all presently registered use patterns the applicator risks are high for the emulsifiable concentrate formulations while the risks associated with the granular formulation are no greater than the general populations risk from dietary exposure. The benefits of diallate use (either formulation) on sugar beets and flax are moderate and all other uses are low.

Applicators of the emulsifiable concentrate formulation may be exposed both dermally and via inhalation as the result of splashing, vaporization, or accidental spills. Likewise during application, exposure may occur both dermally and via inhalation. Table II-10 identifies the dermal risk to applicators of the emulsifiable concentrate formulation as 10^{-4}.

One potential risk reduction measure is to require applicators using emulsifiable concentrate diallate to wear protective clothing. Protective clothing in this instance is defined as rubber gloves and coveralls. These items would reduce the exposure level by a factor of 4 (see Section II.C.1.). This reduction would result in a risk of 10^{-5} which the Agency still considers unreasonable when compared to the low and moderate benefits and, therefore, unacceptable. Therefore, a protective clothing requirement will not be considered as a viable risk reduction measure in this analysis.

Thus the risk/benefit picture for the emulsifiable concentrate formulation is essentially the same for all uses. The applicator risk is high and the benefits are, at best, moderate. Since the risks outweigh the benefits in every case, the Agency must consider regulatory options for reducing the risks associated with the emulsifiable concentrate formulation, in particular, the high applicator risks.

From this analysis the Agency concludes that the high risk involved in the use of the emulsifiable concentrate is unacceptable when considered against the low to moderate benefits of all emulsifiable

Table IV-1. Applicator Risks versus Economic Benefits of Diallate

Uses	Applicator Risk: Emulsifiable Concentrate	Applicator Risk: Granular	Economic Benefits (c)
Sugar Beets	High (a)	Low	Moderate
Flax	High (a)	(b)	Moderate
Lentils	High (a)	(b)	Low
Dry Peas	High (a)	(b)	Low
Minor Uses			
Barley, Potatoes, Safflower, Soybeans, Corn, Alfalfa	High (a)	(b)	Low

(a) High Risk $\geq 10^{-4}$
(b) Although not registered for these uses the applicator risks would remain low if registered.
(c) Benefits analysis did not evaluate the individual benefits of the two formulations.

concentrate uses. It also concludes that this risk can be reduced to the acceptably low dietary level if the emulsifiable concentrate formulation is replaced by the granular formulation. Therefore, the Agency will examine the feasibility of cancelling all diallate emulsifiable concentrate formulations in its regulatory options.

For sugar beets (the only use for which the granular formulation is also registered), the risk/benefit balance for the granular formulation is shifted favorably. Risks become low because of significantly decreased applicator exposure and benefits remain moderate because the cost and effectiveness of granular diallate are approximately the same as the emulsifiable concentrate. Based on this finding for sugar beets, the Agency assumes that this more favorable risk/benefit balance could be achieved if the granular formulation were registered for all of the other uses.

D. Regulatory Options

With regard to the emulsifiable concentrate products of diallate, three basic regulatory options have been developed for consideration:

1. Continue emulsifiable concentrate registrations.

2. Cancel emulsifiable concentrate registrations immediately.

3. Cancel emulsifiable concentrate registrations effective in two years.

Options 1 and 2 represent an absolute regulatory response. For Option 1 it means that sale and distribution of diallate emulsifiable concentrate products are unconditionally continued. Option 2 on the other hand means that sale and distribution of these products are prohibited effective as soon as the decision becomes final. Option 3 represents a decision to phase out the emulsifiable concentrate formulations to permit time to extend the registrations of granular diallate to uses where it is not presently registered.

1. Option 1: Continue Emulsifiable Concentrate Registration

This option would return emulsifiable concentrate formulations of diallate to the registration process, and they would be retained as effective means to control wild oats in sugar beets and other crops. By adopting Option 1, the Agency would conclude that the benefits associated with the use of emulsifiable concentrate diallate outweigh the risks and that allowing its use would not result in unreasonable adverse effects.

Under this option, the potential applicator risks of 10^{-4} resulting from inhalation and dermal exposure would not be reduced. There would be no adverse economic impacts associated with Option 1 because use of emulsifiable concentrate formulations would continue. By choosing this

option the Agency would conclude that the benefits would outweigh the risks of continued use.

2. Option 2: Cancel Emulsifiable Concentrate Registrations Immediately

This option would eliminate all uses of emulsifiable concentrate diallate thirty days after the final Agency decision. By adopting Option 2 the Agency would conclude that the risks associated with the use of emulsifiable concentrate diallate exceed the benefits, and result in unreasonable adverse effects.

Under this option, applicator risks resulting from inhalation and dermal exposure would be reduced to the same magnitude of risk as the general dietary risk. Cancelling all emulsifiable concentrate registrations immediately would imply that risks outweigh benefits.

The economic impact which result from the immediate cancellation of diallate emulsifiable concentrate formulations on sugar beets is estimated to be more than $3 million (Table III-1). The benefit analysis did not attempt to identify the impact of the individual formulations. However, most of the impact will result from the cancellation of the emulsifiable concentrate formulations. This is based on the fact that the emulsifiable concentrate accounts for approximately 85% of the diallate presently used on sugar beets. Flax growers are expected to suffer a $400,000 annual loss while growers of lentils and peas are anticipated to receive an economic gain as expressed in Table III-1.

This option would ignore such factors as availability of alternatives including granular diallate since time would have to be allowed to produce adequate quantitites of this material. It also ignores the time necessary to register granular diallate on flax and other crops for which the emulsifiable concentrate is now registered if the markets demand such action. Lastly, this option neglects to allow time for growers to modify or acquire the necessary equipment to apply the granular formulation.

3. Option 3: Cancel Emulsifiable Concentrate Registrations Effective Two Years After the Decision Becomes Final

This option is essentially the same as Option 2. It differs in that it would eliminate all uses of emulsifiable concentrate diallate two years after the decision becomes final. By adopting Option 3, the Agency would indicate its unwillingness to accept the applicator risks associated with the use of the emulsifiable concentrate formulation indefinitely. This option would lessen the impact of immediate cancellation by 1) allowing time to produce the necessary granular diallate to control wild oats in sugar beets, 2) allowing time to register granular diallate on crops where only the emulsifiable concentrate is now registered and where other registered alternatives are not desirable, and 3) allowing time for growers to make necessary equipment adjustments.

Some granular diallate formulations are presently registered for use on sugar beets only in Minnesota and North Dakota. It will be necessary to allow sufficient time to extend the registration of these granular formulations to the western states. While the registered granular formulation with diallate as the sole active ingredient is only registered for use in the non-irrigated areas, other granular formulations with diallate as one of the active ingredients are registered in other geographical areas (western states). Two years should also provide ample time to register the granular formulation on crops now being treated with the emulsifiable concentrate formulation if the market demands it.

The Agency, based on the information available, believes 1) that a two-year time frame is sufficient time for the company to produce the granular diallate required to maintain control of wild oats in sugar beets, and 2) that two years is ample time for growers to make adjustments in equipment necessary to apply the granular formulation (Lewis, 1980).

Because there is no acceptable alternative chemical presently registered for use on flax, cancellation of the emulsifiable concentrate is a major concern. The expected annual economic impact to flax growers is $400,000. The Agency believes that the granular formulation will provide excellent wild oat control with little or no phytotoxicity and is willing to consider a proposal for this use.

Registrants of the emulsifiable concentrate and granular formulations may submit an application for amended registration to 1) convert their emulsifiable concentrate formulation to granular, and 2) expand their granular registrations to crops for which only the emulsifiable concentrate is now registered. The review of these actions will be expedited and should not require additional data.

V. Proposed Regulatory Decision

The Agency proposes to implement Option 3 which is to cancel the emulsifiable concentrate formulations of diallate effective two years from the date the decision becomes final.

Option 1 is unacceptable because the level of risk to applicators of the emulsifiable concentrate formulations remains at 10^{-4} which the Agency is unwilling to permit considering the low and moderate benefits.

Option 2 is also unacceptable. While under this Option the risk to applicators is reduced to the general dietary risk level, it does not take into account the potential impacts that may occur due to the unavailability of adequate supplies of granular diallate currently registered for sugar beet use. In addition it does not permit any opportunity for the registrant to extend the use of granular diallate to those uses where only the emulsifiable concentrate is currently registered prior to complete cancellation.

Option 3 would overcome the disadvantages of both Options 1 and 2. The Agency would welcome applications to extend the use of granular diallate as a replacement for the emulsifiable concentrate and EPA considers a two-year time frame appropriate to accomplish this. At the same time, the two-year time frame permits the production of adequate supplies of granular diallate to meet expected market demand.

Also under Option 3 registrants would be allowed to convert emulsifiable concentrate formulations to granular and expand granular registrations to crops for which only the emulsifiable concentrate is presently registered.

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